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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/555,342	05/26/2000	YUKIO KATO	046124-5025	3974
9629	7590	05/18/2004	EXAMINER	
MORGAN LEWIS & BOCKIUS LLP 1111 PENNSYLVANIA AVENUE NW WASHINGTON, DC 20004			DAVIS, MINH TAM B	
			ART UNIT	PAPER NUMBER

1642

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/555,342

Applicant(s)

KATO ET AL.

Examiner

MINH-TAM DAVIS

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 February 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 11-17, 19-21 and 25-38 is/are pending in the application.
- 4a) Of the above claim(s) 11-14, 19-21, 29-31, 33 and 35-38 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 15 and 25 is/are allowed.
- 6) ☒ Claim(s) 16, 17, 26-28, 32 and 34 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

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DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 15-17, 25-28, 32, 34, primers of SEQ ID NOs:21 and 22 are being examined.

Claims 15, 25 are free of prior art and are allowable.

The following are the remaining rejections.

PRIORITY DATE

Applicant argues that the priority date of claim 34 is, at the very least, November 27, 1998, the International filing date of PCT/JP98/05348, because the present application is a national stage filing of, and therefore identical to, PCT/JP98/05348. Applicant argues that PCT/JP98/05348 teaches primers sequences of SEQ ID NOs:21 and 22.

Applicant asserts that it is unclear what the Office action is referring as “the claimed nucleic acid”.

Applicant's arguments set forth in paper of 02/26/04 have been considered but are not deemed to be persuasive for the following reasons:

The priority date for claim 34 is still determined to be May 26, 2000 for the following reasons:

It is noted that “the claimed nucleic acid “ referred in the previous Office action means the nucleic acid molecule as claimed in claim 34.

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The present application, although is a national stage filing of PCT/JP98/05348, but is not identical to PCT/JP98/05348. New matter has been introduced into the present application. Although the PCT application filed on May 26, 2000 contains 22 sequences, including the instant SEQ ID NOs: 21 and 22, and although the Japanese priority document recites that DNA can also be obtained from chromosomal DNA by hybridization or PCR using a probe or an oligonucleotide primer prepared based on the base sequence and that alternatively, the DNA can be obtained by carrying out RT-PCR using cartilage mRNA, there is no teaching in said PCT application and the Japanese priority document that a nucleic acid molecule is obtained by PCR or RT-PCR amplification using specifically SEQ ID NOs: 21 and 22 as primers.

In other words, the teaching by the Japanese priority date is a generic teaching of how to perform PCR, and the teaching of PCT/JP98/05348 is drawn only to the primers of SEQ ID NOs: 21 and 22, without teaching or contemplating obtaining a nucleic acid molecule by performing PCR, using the primers of SEQ ID NOs: 21 and 22.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, NEW MATTER

Claim 34 remains rejected under 35 USC 112, first paragraph, pertaining to new matter, for reasons already of record in paper No:17.

The same arguments and reasons for rejection set forth under priority date apply here as well.

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REJECTION UNDER 35 USC 112, SECOND PARAGRAPH, NEW REJECTION

1. Claims 16-17, 26, 28, 32 are indefinite for the use of the language "having Rho-GEF activity". It is not clear what is Rho-GEF ".activity"
2. Claim 17 is indefinite because it is drawn to "stringent hybridization conditions". Stringent conditions are not defined by the claim (which reads on the full range of stringent conditions, that is from very permissive to very high stringency). The specification does not provide a standard for ascertaining the requisite degree of stringent conditions and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention and would not be able to determine the metes and bounds of the claims.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 27, 28 are rejected under 35 USC 112 first paragraph, concerning lack of a clear written description of a "complement" of SEQ ID NO:1 or of a nucleic acid encoding a protein having Rho-GEF activity and comprising at least ninety consecutive amino acids of SEQ ID NO:2, for the same reasons of record in paper No:17.

It is noted that a complement could be partial or complete complement, wherein a partial complement could share with SEQ ID NO:1 or a nucleic acid encoding a protein having Rho-GEF activity and comprising at least ninety consecutive amino acids of SEQ ID NO:2 only a few complementary nucleotides.

Thus the claimed encompass unrelated sequences with unknown structure and function.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Rejection under 35 USC 112 first paragraph of claims 16-17, as being enabled for the polynucleotide of SEQ ID NO:1, encoding the polypeptide of SEQ ID NO:2, but lack enablement for a polynucleotide encoding a variant of SEQ ID NO:2, or a polynucleotide that hybridizes under stringent conditions to nucleotides 49-3183 of SEQ ID NO:1, remains for reasons already of record in paper No.17.

Claims 26-28, 32 are rejected for the same reasons, as being enabled for 1) An isolated full length complement of SEQ ID NO:1, or 2) An isolated nucleic acid molecule consisting of a polynucleotide sequence encoding a polypeptide sequence consisting of the DH and PH domains of SEQ ID NO:2, or a full length complement thereof, but lack enablement for 1) An isolated complement of SEQ ID NO:1, or 2) An isolated nucleic acid molecule encoding a protein having Rho-GEF activity comprising at least ninety consecutive amino acids of SEQ ID NO:2 or a complement thereof.

Applicant argues that the Office action of August 26, 2003, is inconsistent. Applicant asserts that the Examiner has acknowledged in the Office action of January 6, 2003 that the methods for replacing, deleting, and inserting particular amino acids to make variants are well known in the art. Applicant argues that in the Office action of January 6, 2003, the Examiner noted that without the function, one would not know how to screen for the claimed variants. Applicant asserts that the function of the claimed variants has been recited in the claims.

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Applicant's arguments set forth in paper of 02/26/04 have been considered but are not deemed to be persuasive for the following reasons:

Contrary to Applicant's arguments, the Office actions of January 6, 2003, and August 26, 2003 are not inconsistent.

A. Concerning the variants of claim 16, Applicant has not taught how to make the claimed variants. Although it is routine in the art to delete or substitute an amino acid from a polypeptide, in the absence of the teaching in the specification of which amino acids to be deleted or to be substituted, nor which substituting amino acids to be used, and in view of the teaching of the unpredictability of protein chemistry, by Burgess et al, Lazar et al, Tao et al, and Gillies et al, all of record, the effect of the deletion or substitution on the polypeptide structure and function could be in such an unpredictable way that one cannot screen for the claimed polynucleotide encoding variants of SEQ ID NO:2, and having Rho-GEF activity without undue experimentation.

The claims read on nucleotide sequences encoding variants of SEQ ID NO:2 , wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the nucleic acid or peptide, as well as insertions and deletions, provided that the resulted variation is up to 15% difference with amino acids 1-374, or 544-737, or 764-854 of SEQ ID NO:2. The specification and the claims do not disclose any limit on which amino acid that is subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. Thus the scope of the claims includes numerous nucleotide sequences encoding numerous structural variants.

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The specification and the claims do not provide any guidance as to which original amino acid(s) that are substituted, or to which type of substitution besides conservative substitution, or which amino acids that are deleted or inserted so that the claimed polypeptide could still has Rho-GEF activity as contemplated.

Further, it is noted that "having Rho-GEF activity" encompasses numerous activity of Rho-GEF, in view that there is no definition of what the "activity" of Rho-GEF is in the specification. It is further noted that Koyano, K et al, 2001, Osteoarthritis and Cartilage, 9, Suppl A, S64-68, only teach a single function of the N-truncated form of chondrocyte-derived ezrin-like domain containing protein (CDEP) (which the same as the polypeptide encoded by the claimed polynucleotide of SEQ ID NO:1), having the DH and PH domain, and encoded by the polynucleotide fragment consisting of nucleotides 1655-2690; that is, a dissociation of H³GDP from GST-RhoA (p.S65, first column, under GDP dissociation assay and figure 4). Thus one cannot extrapolate from a dissociation of H³GDP from GST-RhoA by SEQ ID NO:2 to claiming SEQ ID NO:2 having any activity of a related protein, Rho-GEF, because SEQ ID NO:2 encoded by the claimed polynucleotide of SEQ ID NO:2 is not Rho-GEF, and it is unpredictable what other "activity" of SEQ ID NO:2 is the same as the "activity" of Rho-GEF.

B. Concerning the hybridization species claimed in claim 17, it is noted that even under the highest stringent conditions, the claim encompasses unrelated sequences, with unknown structure and function, which hybridize with SEQ ID NO:1 via a common fragment. Further, stringent hybridization conditions encompass from low to high stringency, wherein under low stringency, it is expected that unrelated sequences would

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hybridize to SEQ ID NO:1 Applicant however does not teach how to make such unrelated sequences, such that they function as claimed.

C. Concerning claim 26, due to the language "comprising", claim 26 encompasses a nucleic acid molecule encoding a protein comprising unknown sequences attached to any ninety consecutive amino acids of SEQ ID NO:2 and having Rho-GEF activity.

Applicant however does not teach how to make the claimed molecules, such that they would encode a protein having Rho-GEF activity.

Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Bowie et al teach that certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). Moreover, protein chemistry is unpredictable, as taught by Burgess et al, Lazar et al, Tao et al, and Gillies et al, all of record, wherein a difference of even one amino acid could dramatically affect the biological activity of a protein.

Thus, in view of the teaching of Bowie et al, Burgess et al, Lazar et al, Tao et al, and Gillies et al, it is expected that the amino acids sequences, that are attached to any

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ninety amino acids of SEQ ID NO:2, could have important influence on the conformation and function of said ninety amino acids of SEQ ID NO:2.

Based on the teaching in the art and in the specification, one cannot predict that additional sequences, with unknown structure, attached to any ninety amino acids of SEQ ID NO:2 would not change the conformation and structure and thus the function of the ninety amino acids of SEQ ID NO:2, in such an unpredictable way, that one cannot screen for the Rho-GEF activity, without undue experimentation.

D. Concerning the complement of claims 27-28, it is noted that a complement could be partial or complete complement, wherein a partial complement could share with SEQ ID NO:1 or a nucleic acid encoding a protein having Rho-GEF activity and comprising at least ninety consecutive amino acids of SEQ ID NO:2 only a few complementary nucleotides. Thus the claimed encompass unrelated sequences with unknown structure and function and Applicant does not teach how to make such sequences.

REJECTION UNDER 35 USC 102 (b)

Claim 34 remains rejected under 35 USC 102(b) as being anticipated by Koyano, y et al for reasons already of record in paper No: 17

Applicant argues that claim 34 is entitled to a foreign priority date of at least the filing date of the prior PCT application of November 27, 1998, and that the recited reference was published in December 18, 1997.

Applicant further argues that claim 34 is a genus, and the prior Japanese application teaches SEQ ID NO:1, and that the Koyano et al reference teaches only a

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single species that is identical to SEQ ID NO:1. Applicant argues that the rejection of claim 34 as 102(a) would be improper, since the priority document establishes at least a constructive reduction to practice of the species invention as of November 27, 1997, before the publication date of Koyano et al reference.

Applicant's arguments in paper No:16 have been considered but are found not to be persuasive for the following reasons:

Rejection remains, because claim 34 is not entitled to a foreign priority date of November 27, 1997 of the prior Japanese application, nor November 27, 1998 of the prior PCT application. Although the species SEQ ID NO:1 is entitled to have the priority date of November 27, 1997, the genus claim of claim 34 is not entitled to the priority date of November 27, 1997 of the prior Japanese application, nor the priority date of November 27, 1998 of the prior PCT application, for the reasons set forth above under priority date issue.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:30AM-4:00PM.

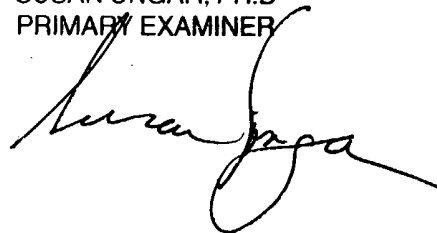
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, YVONNE EYLER can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS
May 08, 2004

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to read 'Susan Ungar', written over the printed name and title.